there was no clinical signal being given, that what we're calling the endpoint, the surrogate endpoint, is a very serious endpoint. It's the absence, complete absence of the adhesion, so it's not just that they picked a couple of scales that seemed to work. That's the way I'm interpreting what we're saying.

DR. BLANCO: Any other comment?

MR. : I think I would like to get a little clarification from Dr. Schultz. I think I heard in your second scenario that if it's equivocal, then you would be interested in the panel's insistence on postmarketing studies. If it's equivocal, I would insist on that premarketing.

DR. SCHULTZ: Well, since I have to defend my own statement, I don't want to be hoist on my own petard here. My intent of saying that is because the outcomes of these studies range from very clear to less clear, and how do you get products that are less clear but may have multimodal benefits, how do you get them approved, under what conditions, rather than projecting them?

So those, those comments about manufacturers expecting a postmarketing requirement would be those that are on the lowish end of the efficacy and those in which part of the labeling has included the use of nonhuman data, for instance, because there's no other way to do it. The

clearer the picture, the less the need for postmarketing studies; the more muddy the picture, the more limited the labeling for which if the manufacturers want some of those limitations taken off.

If you've got a mild adhesion reduction product that you're willing to put on with conditions, then it's--there will be all these things: Has not been shown to improve pregnancy; has not been shown to improve pain. If you want some of those restrictions, you know, lifted out of your labeling and modifications, then that's where those studies come in.

If you have some very clear endpoints, it wasn't my intent that when a sponsor proves a clear endpoint, such as adhesions to the abdominal wall, that, to me, if you prove that, you're done, because that's a clear benefit. Enterotomies, getting in, et cetera, et cetera.

And so I want to just, you know, make my intent very clear, that as we get down into some of the muddy things, that you could look back, that one panel on a good day might have approved it; another panel said it's not clinical enough; that the mechanism of giving people for safe products a break, would be expected to do some more work--

DR. BLANCO: Well, I'm going to disagree with you.

DR. SCHULTZ: Okay. You're the boss.

DR. BLANCO: I think probably--no, I don't even get to vote. What are you talking about? I'm just mouthy, that's all.

I'm going to disagree with you because, and I think the panel will agree with me and disagree with you, that we sit here and we face the same thing about putting penicillin in the chest every time we try to evaluate a PMA. And when it comes out and it's real clear, then it's real easy. Okay, it's safe and it's effective and so it's real easy to vote on it.

But unfortunately we get a lot of those muddy PMAs with lowish type of benefits, and just because they're safe doesn't mean that they ought to go out on the market, because we've all seen lots of things that are "safe" but then get used off indications, and all of a sudden they become totally unsafe and create all sorts of problems. And in OB/GYN we have a whole litany of things that I could go into and don't because I will go off on a tangent, but that belong that way.

So I disagree with you fairly strongly, and I think so will the panel, that if you've got clear data, by golly, you've got clear data and you don't need to do anything else. You know, if you want to improve your indications, you want to say pregnancy, you want to say all the other things, well, then, bring in the data and maybe

you can be doing that, you know, postmarket or something like that.

But if you've got muddy data and it kind of shows maybe a little benefit but not very much and is very questionable, I'll tell you that this panel will likely vote it down, and I would recommend that they vote it down because that's not the kind of thing you need to do. You need to bring, industry needs to bring premarket data that clearly shows a benefit. Okay? A clinically significant benefit, with safety. And that's our charge, and that's what they tell us we're doing here, and that's what we're going to do. Okay? And I feel about it just like you feel in your story. As a matter of fact, I'm going to borrow, if you don't mind, your story about penicillin in the chest.

Does the panel want to weigh in on that?

MR. : I think if it's going to be part of a multimodal methodology, then it should be researched in that way, too.

MR. : Well, the problem with that, let's say you go back to 5FU and Lovamacel for colon cancer. 5FU, in and of itself, is not very effective and probably couldn't get approved primarily today. But 5FU in combination with Lovamacel has a pretty good clinical effect with patients with colon cancer, and the fact that 5FU had some effect, and it was all done prior to the current method

of doing this, is one of those types of strategies where you can see maybe preventing effective synergistic strategies for the patient that other people won't even know about because it never even made it to market. Well, this works some; what if we put it together with this? They'll just die on the vine. And I understand your point completely.

DR. BLANCO: I think we're rehashing the same thing, so we're going to move on. I mean, I think we have basically, unless one of the panel members wants to disagree with me, that they don't feel that's their viewpoint, then let's move on, because you've stated it and I've stated it. So let's go from there. Happy with number 2 now, Dr. Schultz?

DR. SCHULTZ: I am.

DR. BLANCO: It's exactly 3 o'clock. I'd love to get through more. What's the panel's prerogative? Keep going? Let's keep going.

Number 3: There are many potential types of adhesion barriers: gels or sprays applied to a general area, a sheet applied to a specific area, or solutions which freely diffuse throughout the abdominal-pelvic cavity. Keeping in mind the various formulations of adhesion barriers, please discuss the appropriate patient population, i.e., level of adhesions at baseline, clinical presentation, surgical models, and methods of follow-up--functional,

second-look laparoscopy, et cetera--for the following:

(a) Reformed versus de novo adhesions;

(b) Site-specific application, i.e., a tubular, spherical, or flat anatomical structure, and the ability of a study or a site-specific application to support an indication for application to other areas in the abdomen and other types of surgery; and

(c) Gynecologic versus general abdominal surgical indications.

All right, anybody wants to start with 3? Go ahead, Nancy.

DR. SHARTS-HOPKO: I want to make a comment that's not exactly applicable to (a) through (c), but 3 is the best place to make it. When I read through this draft guidance, the only thing that I worried about, that I didn't think was addressed anywhere, and I don't in fact think is appropriate to lay on sponsors in a premarket approval application but I want to tell Dr. Schultz, is we're coming up with new chemical compounds that we're going to stick in people.

And in my practice in the last 10 years with women with HIV and women with multiple sclerosis and various other kinds of autoimmune and chronic illnesses, I've become aware of more and more women whose immune systems crash on them in mid-life because of cumulative chemical exposures. And so I thought to myself, "Hmm, we're sticking a nice new chemical

in their abdomen, and who's to know what would be the long-term effect of that?" I don't think that can be studied in a premarket study, but I think it's something somebody has to keep an eye on.

DR. BLANCO: Well, I think the issue is, a lot of those things don't really become apparent until you have widespread use of the product.

DR. SHARTS-HOPKO: Years later, yes, years later.

DR. BLANCO: So what you're saying is that as part of application of some of these products, they may need to keep track of that over years.

All right. Any comments on 3? Anybody want to tackle this one?

DR. CARSON: Well, I'll attempt it.

DR. BLANCO: Thank you, Sandy. I appreciate it.

DR. CARSON: Yes. Let me go in reverse order, though, because that seems to me a little bit easier.

First of all, I think that gynecologic and general abdominal surgical indications must be separated, when it comes at least to adhesions. And although you made the point that it is one cavity, that is true, certainly once the patient even sits up or gets out of bed, the abdomen in adhesion formation is very, very different. If you have a barrier, one of the liquid barriers, using, certainly using some principles of osmotic and dilutional anatomy, the water

will settle in the pelvis and you'll have treatment for far longer than you will in the upper abdomen, once the patient sits up, so I think that abdominal, general abdominal surgery must be separated from gynecology.

In terms of site-specific applications, I think that there are groups of organs that can probably be clumped together. For example, I think both--I don't think you have to look at the right ovary and the left ovary separately. I would think that the ovaries are the same. I think the uterus and uterine adhesions probably should be considered as a separate site. Similarly, I think tubal adhesions should be considered a separate site, and I think abdominal wall--like adhesions to the site of incision should be separate from peritoneal incisions.

And then (a), reformed versus de novo adhesions, I guess this refers to what kind of surgery or patients. It seems to me that de novo adhesions are best studied in the patient who has never had surgery before, that is, has had only one prior surgery, because--and I gather this is what is meant by de novo adhesions--I think that if you're talking about a patient who has adhesions from a prior surgery, and these are lysed, then going back in that patient and looking at a different site I think biases that observation, because we don't really know what kind of systemic factors are involved in adhesion formation. Once

you have adhesions and lyse them, you may invoke a different set of cytokines that may be important in de novo adhesion formation elsewhere. So I would think that the de novo adhesions really should be in the patient who is having her second surgery and not thereafter.

And reformed adhesions I think are better in patients who have had an adhesiolysis, had an adhesion cut, and those adhesions are reformed. And unless I am--I might be misunderstanding exactly how you mean those, but I gather that's what you mean by those types.

DR. BLANCO: Thank you. Any comments from anyone else?

MR. : Well, my take on de novo would be adhesions as a result of an operative procedure or in a location not previously operated upon, so that I would slightly disagree in the sense that if you went in and performed a myomectomy and then you had your two groups, control and treatment, and you looked back in and there were new adhesions there, then that would be a new adhesion; or in a location where there had previously not been an adhesion, and where you had previously not performed surgery. That, to me, is my take on de novo.

MR. : You may find it hard, if you for instance did a pelvic study and one of the findings in the pelvic study was that the number of small bowel adhesions

were reduced, and so if you generate findings such as that, you make it hard to realize that you've stopped a--that stopping a uterus to small bowel adhesion is different than stopping a small bowel to uterus adhesion.

And I think that you have to look at the products individually. You have used solutions as an example of why maybe a pelvic study you can't generalize to other parts of the abdomen, but you could almost imagine a film barrier that is working on a site, that that is a peritoneal surface, it's not going to move, it's working on that site, and that they are all peritoneal surfaces and you should be able to potentially generalize. Again, a spray gel, if you say, "Where does the pelvis end? Does it include the cecum? Does it include any of the small bowel? Does it include the omentum?" I mean, you run into some very, very artificial distinctions.

But if you do your study in the pelvis, then I think that you should also be given the opportunity to provide rigorous, nonhuman data of why your claim should be expanded. And I think that there should be enough latitude that there should be other ways of providing data that allow a sponsor for an abdominal and pelvic claim, because it's hard to say you're never going to do a study where you never got an omental adhesion, you never got a colon adhesion, and you're ignoring the fact that that's all part of the abdomen

as well. And I think that if studies are limited in their design, then there should be additional mechanisms for getting the broad abdominal-pelvic claim that the manufacturers are really looking for.

MR. : I think the issue, I think you said in the beginning, part of the problem I think in trying to give this type of advice is that if the devices are so--you know, devices, they're not even devices, you know, they're cloths and gels and liquids, and everything is so varied that you really have to look at it individually, as you said originally.

You know, the cloth that you're going to put over a fallopian tube that you've reanastomosed, I guess you could put it over an ileal reanastomosis, but you're not going to put it all over the abdomen or below, you know, probably below the wound. So I think you have to take each of the products according to what is its intended use and what is its makeup, to try to decide whether, you know, you can extend an indication or not.

I mean, I would think that in terms of preventing adhesions, if you put say something that was similar to a cloth or something over the tube, if you did that over the ilium, you could probably aspect similar results. You wouldn't be, you know, thinking why would it be--why it might be different, although I guess bowel flora might be

different and might--

DR. CARSON: Or standing up, the fluid might wash that little barrier off.

MR. : But I think if you showed in a preclinical model, saying "There is reason to believe that our animal studies, that what we showed clinically to the tube, you know, our preclinical studies, will work on the bowel," then that would be a mechanism by which the broader indication could be given.

MR. : Well, I guess my question in this whole thing is basically, are we discussing the fact that adhesion formation is different in different sites, and that therefore the different, you know, barriers are going to act differently at different sites?

You know, if we assume that adhesion formation is the same in all sites, then obviously all you're arguing about is basically then, you know, will the device or fluid or whatever you're going to call it, is it going to effectively do its job in the site that you're trying to apply it to, and that's a whole different issue.

I mean, to me you've got two issues here that we're talking about: Number one, is adhesion formation in the pelvis the same as adhesion formation in the anterior bowel wall? And do we have any reason to assume that it's not? You know, and that the device is going to work the

same both place. Then the next question is, you know, would be establishing that the device can work effectively in the site that you're trying to apply it to.

MS. : Well, I think that when you say is adhesion formation the same, I mean maybe in terms of biochemically how an adhesion is formed, it probably is, and how they revascularize.

However, there are a lot of variables, like for example when you do a myomectomy, there's a lot of tissue damage, there's a lot of cautery, there are many sutures, there's a lot of bleeding, as opposed to an appendectomy which is really a rather quick procedure and not a lot of tissue damage. There's bacteria, and you have different, perhaps different factors, but the procedures are different enough that you can't say that the--and because the inciting factor is different enough, you can't necessarily say that the incidence of adhesions would be the same.

That's why the sites have to be different, because the handling is different, the suture and the mechanics are different and therefore--and not only that, but the site may affect the device. For example, again, in the pelvis if you put a barrier on the uterus and then you have a lot of peritoneal fluid and you're sitting up five hours after surgery, there might be a lot of fluid that just floats that device right off the uterus, and therefore you're having no

effect at all. Or maybe you are having an effect just from the fluid. So I think that the sites have to be considered separately.

MR. : Yes, but then you're--now you're adding surgical technique into the product. Okay? And--

MS. : Well, you can't help but do that.

MR. : Well, but the question is like, "Do you believe in closing the abdominal peritoneum or do you not believe in closing an abdominal peritoneum. Certainly adhesing bowel to closed peritoneum is different than if you've got small bowel adhesed to the underlying rectus muscle. I mean, that's--I mean, so that, you know--but--and again, you know, with the pelvis. But what I understand is, when you're looking at adhesing the peritoneum against peritoneum, is it any different in how are we judging the anti-adhesive device. So now we're down to, how does a surgeon fix things, you know, and--

MS. : Well, no. What I'm saying is the site--

MR. : --and how does the site react to cautery effect.

MS. : Right.

MR. : How does the site react to different things? And, I don't know, those are other questions. Do we ask that in a preliminary study, as to

how--we have not talked about that yet--as to how do these devices work in tissue that has been damaged by cautery? How does it work by tissues that have been sutured? I mean, those are whole different issues because they are obviously long-term issues, you know, where the healing process is extended or you're dealing with necrotic tissue.

MR. : This is a quagmire that I don't know that we should get into. All myomectomies are not the same. All appendectomies are not the same. So if we start to get into the specifics of an operation, I mean, it's going to be very difficult for us to come up with, you know, appropriate data. I mean, I take 12 myomas off of a uterus, and use cautery and a certain kind of suture, it's different from removing one and not using any suture or not using cautery or using a laser of some kind. I don't know. I mean, it's a quagmire and I don't think we need--I think site-specific information is enough, and if we get into technique, it's going to be a real quagmire that we can't resolve.

MR. : Well, I'm also concerned about something else, and this comes back to that illustration of that 32-year-old patient who had a cystectomy but ended up with a significant bowel adhesion that we were shown a picture of, in a location where no surgery was performed.

My specific point is that while we can gain a

certain amount of assurance that if a device, if applied in the pelvis, can be shown in animal studies to remain in an abdominal site if applied, I'm not so sure that you can use a solution, for example, in the pelvis in gynecological surgery and then advertise it to reduce intra-abdominal adhesions unless you have data that it gets there and in fact does that, without doing the studies, without doing the due diligence.

MR. : The physiology of fluid movement through the abdomen has been studied, and it's amazing how much fluid moves through the abdomen. And I think part of the problem is that I think optimal adhesion strategies will be multimodal.

Certainly if you had put a film on the ovary that was operated on, it would have no impact on a de novo adhesion at a remote site. That would be ludicrous to believe that. But perhaps in multimodal strategies where they had used a solution to precoat and a site-specific thing, then maybe you can eliminate the kinds of adhesions that we saw.

And I think, you know, it goes to this quagmire of what are you trying to accomplish with any particular product, but we do know that there is extensive fluid motion throughout the abdomen and that the claims have to be based on, if you want to prevent remote adhesions, you better make

sure that the fluid is distributed effectively throughout the abdomen.

MR. : That's all I'm asking. I just want to see the effects. I'm not saying that it doesn't happen. I'm just saying that if a manufacturer wants to make that claim, show us the data.

You see, the problem that I had was that they said, "Yes, we looked at the upper abdomen at the time of laparotomy. Obviously we couldn't do that at the time of laparoscopy, and yet we want the indication." So it was a it inconsistent.

MR. : So you think those goals are achievable, is what you're saying?

MR. : I'm saying, yes, they should be achievable.

MR. : Well, I think that it's reasonable. I think the problems you're going to run into are things like interbowel adhesions and stuff like that. But certainly if you can see the separation of the intestines and omentum from the abdominal wall, and you have part of your protocol that you have distributed this material because you want that as part of your claim, then you have an opportunity to collect that data.

DR. BLANCO: I think the panel has come out, essentially there has to be the data to move the indication

from site-specific, from site-specific indication, seems to be the panel opinion, from what we see.

Yes, Dr. Schultz?

DR. SCHULTZ: Could I ask a specific question? I think Dr. Schwaitzberg made a suggestion that some of that data could in fact be collected in animals, and I'm not sure that that was directly addressed. We did not address that specific point.

You know, we talked about animal, using animal data as preclinical data. Elisa described a lot of the important information that could be collected. But I think what we're talking about now is sort of closing the loop and going back from the human data to the animal to extrapolate from one site and one indication to another, if I understand what you're saying correctly.

MR. : Right, and the example is the tubal clinical study, but it's not practical to go back and look at a small bowel anastomosis, there's not a practical way of conducting a clinical trial. Would you feel that it would be reasonable that if they showed it in the tubal anastomosis and very clearly showed it in the non-human model, that you would be satisfied that you could move from the tubal site to other remote sites?

MR. : You know, I think that if we do this site-specific thing, we have to do it site-specific.

You have closed the door for a lot of applications. You're saying, "Wow, we can use this stuff in the pelvis," but there's no way of basically clinically evaluating whether the stuff really is efficacious as far as keeping omentum and small bowel off our anterior abdominal wounds. And, I mean, so we've closed the door for the use for something where it may be really advantageous, but no way to collect the data.

MR. : Well, no, the issue is not--the issue is, say that someone has a cloth that you put over the tube and it prevents adhesions, and you clearly show it, show it in humans. You now want to use it for small bowel reanastomosis, and the issue is, do you have to go back and do that on humans and demonstrate it again, or is animal data sufficient to extrapolate from one site to the other site?

My answer to that I guess would be that there needs to be some evidence that it's data that can be extrapolated from the animal to the human. I mean, in other words, not all animal models really reflect what happens in the human necessarily. So I think it depends on how well the animal model correlates with the human to some extent, and I think human data is always going to be stronger information than animal. I don't know what--what else does the panel--

MS. : I just don't know enough about wound healing or adhesion formations in animals. I do know in rabbits, you have to do a lot of tissue damage to get adhesions in rabbits, but I don't know anything about--and obviously fluid dynamics in the rabbit is different than in an upright animal, but I don't know anything about--

MR. : If you want to do your work with primates, then you would look at the primate animals. And actually you wanted to make some comments about animal models, I believe.

MR. : And I think that's valid, but if you're going to go into site-specific, whereas there's no reason to suspect that it wouldn't work in other places in the abdomen, and you were provided some measure of comfort that the concept that it's a global effect is reasonable, then that gives you an opportunity to improve your comfort level.

We have run a primate colony for over a decade, and our primary primate is baboons. They are not hard to obtain. They are not more expensive than using a canine model. In Massachusetts they are only--a dog in Massachusetts costs about $400 and a primate is about $1,000, so it's not orders of magnitude more difficult.

I would agree that there are less centers that do primate work, but the nature of approving multiple

reoperative surgeries are based on the indication and the need, and a three-operation model in a baboon would clearly be approved with an appropriate clinical indication, and a two-operation model to look at de novo adhesions would be clearly approved in baboon models. And I would beg to differ very strongly that primate surgery is not easily accomplished because, compared to doing a human clinical trial, it's way easier.

MS. : Well, let me ask you, in the primates, are the postoperative incidence of adhesions after upper abdominal surgery the same as in humans?

MR. : Well, I don't think it's been studied to the satisfaction--I think this is one of the opportunities for the manufacturer to prove his or her point. You can prove that point. It's a provable point one way or the other. And you've been very concerned about the upright dynamics and the fluid, where the fluid is going. Your best chance to show that is in an upright animal, if you want to show that.

But I think again it goes back to what we have been saying, is that the narrowing of the indications to site-specific means that we don't believe that--we believe that healing here is different than healing there. There is no scientifically valid data to indicate that healing a tube is a lot different than healing a piece of bowel. They are

both mucosal, they have serosa, you know, there is bacteria in the tubes. I mean, there is bacteria everywhere.

And I think you get comfort by having manufacturers include additional data, but there is no reason to believe primarily that the healing and the prevention of adhesions in different sites, short of some of the gravity issues, is different in different places of the abdomen.

MR. : But wouldn't you agree that there are orders of difference in the amount of microorganisms in the bowel as opposed to the oviduct?

MR. : Well, yes, to a certain degree. But again, we don't even know what is clinically relevant. If you a bowel prep in a colon, you've greatly reduced it. If you're doing a proximal small bowel, the difference in bacteria is different than in the distal, the distal small bowel. We don't see clinical infection around anastomoses. So even if there are some flora, there doesn't seem to be a clinical impact. There's not a lot of abscesses.

I mean, if you had a situation where abscess formation around an ileoileostomy was very high, then yes, you know these flora are meaningful in some way, and you have a basis for saying, well, that's different than the tube. We don't see infections around the tube, we don't see infections around the ileum, we don't see infections around

gastrojejunostomies very commonly, and I think that's the point.

DR. BLANCO: You've made your point. Let's have Dr. Silkaitis--I'm sorry if I mispronounced your name. I apologize.

DR. SILKAITIS: That's all right.

DR. BLANCO: You wanted to make some comments about animal studies, and then if it's agreeable to the panel, I'd like to hear Dr. Diamond's opinion on usage of animal models to move from one site to another site. So, Mike, if you would be thinking about that.

Yes, sir?

DR. SILKAITIS: Before I request Dr. Wiseman to come up and help us talk about the primate topic, I did want to mention for the benefit of the panel members that FDA does have the discretion to evaluate expanded labeling into other areas, and they have done that, as was seen with Seprafilm, but they have also done it in other areas by other--in other divisions, whereby either animal data or the fact that they would have probably a half a dozen patients evaluated non-randomly to address some of the concerns of technique.

So that if the science is there, such that it's reasonable to conclude that the pathophysiology or the physiology of the adhesions is the same in the peritoneal

cavity, well, then--and it was studied in the pelvic cavity --then the extrapolation to the abdominal cavity may mean just doing some animal studies plus a few patients, just to make sure the technique is okay, and not a full blown randomized clinical trial. There have been examples that other products have been studied in that way and approved with much broader indications for use, so I just throw that out for the panel members.

I would like to invite Dr. David Wiseman.

DR. BLANCO: Why don't you, Dr. Wiseman, why don't you please restate your name and affiliations, and we'll have Dr. Diamond after you.

DR. WISEMAN: Thank you. Thank you for inviting me to speak on this point. My name is David Wiseman. Again, my company is Synechion. I, together with probably four or five other people in this room, I would think have conducted probably 90 percent of the world's animal studies in adhesions. That probably is not an exaggeration.

Clearly adhesions are a very difficult problem that we've been grappling with today, and the charge that the FDA has is to assess the probable benefits versus the risks of any particular product. And because of the problems that we've been discussing, this site versus that site, I think many of us have come to the conclusion that we have to address different aspects of a product's indication

using different kind of animal models.

Until recently we have had no correlations between animal models and clinical, the results of a product's efficacy in an animal model versus it's efficacy in a clinical model. Recently I have published, in a book that Dr. DeZiarga edited, some correlations between a particular version of the rabbit uterine whole model in about 10 products and their clinical outcome--comparing animal studies, the outcome in animal studies with the outcome in clinical studies.

So we know that in rabbits, at least in gynecologic models, there seems to be a fairly good correlation between the outcome in animal studies and the outcome in human studies. That correlation is limited, obviously, by the parameters of the studies, namely, these were all gynecologic studies. These were not general surgical types of studies.

The second category of studies that Dr. Harvey, I believe, listed was the model which again is done in rabbits, Again, there is some correlation, although not as strong, between the results, the efficacy of products in those models versus the efficacy in humans. And not only is it not as strong, but the model tends to be--tends to show an overestimate of the product's efficacy.

I also looked at other models. There are two

papers published, I believe, in primate models. One is Sites and one is Groh. I can provide the references later. And it's very difficult to make any kinds of conclusions about the correlations of those models in animals versus clinical outcome.

What we're finding is that there doesn't appear to be any rational basis as to why there is or there is not a correlation. It's merely an empirical basis. So to set an absolute requirement that we need to do a primate study, I'm not sure we have good reason to do that at this point.

However, the way I would attack the overall problem is to look at a battery of studies, types of studies, in perhaps rabbits or dogs or pigs where we looked at different organs, so we might look at gynecologic organs, we might look at upper abdominal locations, we might look at the product's efficacy around an anastomosis, we might look at a product's safety around an anastomosis, even though the model may not be capable of addressing efficacy. Okay? And by doing all of those things, we can get some kind of idea of what is likely to happen.

Now when we come to the clinical situation, because of the problems that we have described earlier and difficulty in conducting certain kinds of studies, what I think some of us have come to the conclusion as proposing is that we do whatever clinical study we can do, whether it's

the gynecologic study or the types of studies that Dr. Schwaitzberg was describing, but in addition we could supplement that with a safety type of study, say in patients undergoing elective bowel anastomosis, where we do not expect to get any efficacy data because we're not going to do second-looks in those patients.

However, we can follow them for two months, three months, four months or whatever, to see if they have any problems with the safety, with infection or wound dehiscence and so on. And this way, what we have done is, we have assessed the risks, we have discerned that the product is indeed safe even in those situations where we are unable to assess efficacy, and in places where we are able to assess efficacy, it is efficacious.

And on the basis of two things, number one, the conduct of animal studies and, number two, the likelihood that adhesions--the pathobiology of adhesions is essentially similar throughout the pelvic, throughout the abdominal cavity; and actually a third one, that the mechanism of action of these agents, namely, they are barriers, we could probably address in labeling, some kind of statement that says this product is indicated for the reduction of adhesions and it's based on clinical studies performed in XYZ type of procedure, but on the basis of ABC types of procedures, the likelihood is that it is safe in these other

procedures, but its efficacy has not and could not be demonstrated.

DR. BLANCO: Thank you.

Dr. Diamond, would you mind saying a few words about animal models?

DR. DIAMOND: My name, again, is Michael Diamond. A couple of points I guess I would make.

I find Dr. Schwaitzberg's idea of primate models very appealing, and appealing from the point of view of standing up as opposed to different positions with most of the other animals that we utilize. But I'm not aware of good evidence that a primate is any more reproducible of what we see in humans than is any other species, and therefore I don't know that I would specifically advocate it as a model, as that.

I think, as Dr. Wiseman was just saying, that in certain circumstances, for instance bowel anastomosis, there might be a role for animal studies as a first line, at least to look and see whether there is an effect of a device or an adjuvant which may be a complication in those settings. From that point of view, I think it is helpful.

But by and large I think of animal models as guidelines, as just that, as models which can give us some inferences but which--where the pudding still remains the human clinical trials. Dr. Wiseman, as he was mentioning,

has put together some very eloquent studies trying to look at the world literature of animal studies and compare it to clinical outcomes as has been defined by human clinical trials, and I don't think you can do it better than David has done, but there are problems with those studies.

First of all, he has had to group, for example, uterine horn models in rabbits, which is probably the most common model done by different investigators, different times, and a uterine horn model is not necessarily a uterine horn model. Even when the scoring system is the same, having seen what different people say is a uterine horn model and their scoring systems, if I go from one place to another, they can be very different. And unless you're actually there and see it or have seen the pictures, and even pictures can be misleading, unless you really see it, it's often very hard to equate one with the other.

Furthermore, the other major problem with--and I've seen David's analysis and I've shared this with him before, so it's not new to him--is that the only clinical results that have ever been published on anti-adhesion adjuvants, these large clinical trials to my knowledge are good ones. Now I know of a lot of other studies that have been conducted, but the results have not been published, and I am left with the assumption those probably did not show good results. And so it's hard to make correlations of

animal studies with human clinical trials when we don't have the clinical trials that haven't worked as well.

And it further gets complicated by the fact, as has been alluded to today, that there are so many factors that may go into a human clinical trial that you could have a great product that really works, but if you don't design the trial properly or pick the right patient population or use the right scale of measurement, you may not be able to see an effect; or, conversely, you may see something that's not really there.

And so I think there are a lot of limitations. I think animal studies are good to be suggestive. My own personal belief is, there is something to be said if you have good results in one animal model, to do something in another model, probably in another species, but to have two models which give you confirmative results. But then it's my own personal opinion that you need to go to clinical trials in order to find out whether there's really something there.

DR. BLANCO: Thank you. Any comments from the panel? Does the panel want to make any comment about the use of animal models instead of clinical data, for moving from one site to another site? Yes?

MS. : Well, I just wanted to make a comment on one of the things that you said, Steven, about

there not being clinical evidence about site versus site. Dr. DeCherney actually cited three studies.

One, adhesions after myomectomy, he cited a 60 percent de novo adhesion formation; and another in 40 percent de novo adhesion formation with adhesiolysis over the fimbria. So that is a site difference in scientific collected data. Also he cited a prospective randomized trial in which Hyscon and saline were used, and found no difference in preventing ovarian adhesions but a difference in preventing cul-de-sac adhesions, so there are site differences.

And, second, I would also say that I would think that animal studies right now might play a role in calculating sample size and helping with power calculations in humans if the prevalence of adhesions after the surgery are similar. But I'm not sure, I haven't heard whether anybody really knows that adhesion formation after certain--at certain sites in the primate is similar than in the human. And I would see their role right now as help in power calculations, but certainly not as a replacement for clinical human trials.

MR. : Well, there is Alan's data that the number of--the absolute incidence can differ. There is no data that the mechanism of how these adhesions forms is different, and he also said that there was a correlation,

although not one-to-one, if I can paraphrase him--I'm trying to quote as accurately as I can--of the development of adhesions in the upper abdomen compared to the lower abdomen, implying that there was a generalizable phenomenon to that.

You know, these--as you collect data, you know, it's very hard to--you know, numbers change, but I don't think he meant to imply that there's a difference in the mechanism of whether a product is likely to be effective, whether you're coming down from 60 percent to 50 percent or 40 percent to 30 percent. I don't think that was the implication.

MS. : Not mechanism but effect.

MR. : But the effect may change, but he didn't seem to imply that there wouldn't be an effect from one site--

DR. BLANCO: Let me--again, I think we're hashing the same thing. I think the panel pretty much has come in on the side that site-specific is probably the way to go, and we're really looking at animals. And I gathered from the panel's behavior that they have some hesitation in saying that animal data can replace human data. Am I expressing the panel's feeling?

MS. : Yes.

DR. BLANCO: So I think that that's where we lie

in that answer, so we'll move on. Even though we may never be able to move from here with the snow, we do want to finish at some point. Okay?

Number four, please discuss the pros and cons of different methods for masking a clinical trial: Having the primary surgeon be blinded to the product used; having a second surgeon who is blinded to the treatment perform the second-look laparoscopy and adhesion scoring; using video tape at second-look laparoscopy and a third party to score the adhesions; other possible methods of masking a study.

Any comments? Go ahead, Dr. Carson.

DR. CARSON: Well, practically all of these methods are really very difficult. I think that practically the patients--having done these, the patient wants their own surgeon, and I think that the--I think probably, personally, the best thing to do is to train the investigators to, one, do a narrative videotape in a very similar way in every surgery, and then have an independent observer listen to the narrative and blind that observer. I think that probably that's the practical compromise for getting the best data in way that's reasonably objective.

DR. BLANCO: Jerry?

DR. SHIRK: I guess the disadvantage of being an observer of a videotape and being the surgeon is basically your loss of tactile sense and the orientation. The

advantage that the operator has is that he or she is, first of all, oriented because of the way they're handling the camera. Secondly, they also have, you know, some tactile feel as to what's going on.

And so that I think there's a definite bias built in at that point right there. So I think it's going to be really difficult to basically have the operator score it and then come back and get a sonar from somebody who's observing. You know, if you use two observers and average the score, it might make more sense than to use, you know, an operator and an observer.

DR. BLANCO: Well, but there are different ways. I mean, I've heard pros and cons on the video, and I'm not sure yet which side it would fall on. But I think if you're going to use a video, you would have to have some validation that you can reproduce the results that you're getting from the video, and I think you also have to have a video that's made in some standardized fashion, no matter what you find. You have to have some standard total look at the area that you're looking for some period of time, to be able to get it to be useful.

DR. SHIRK: Oh, I would agree there, but what I'm trying to say is that I think if you used two people that were just observers to grade the video, and then you used their--I mean used a standardized method and then used two

observers rather than one operator and an observer, that you're going to get much more consistent--you should get much more consistent grading than you're getting using the operator and the--and an observer, just because of the difference in the whole sense of what's going on.

DR. BLANCO: I think Dr. Schultz wants us to refer back to the document--

DR. SCHULTZ: Well, actually since I maybe tend to lengthen discussions, maybe I can shorten this one by a simple suggestion. We've listed a number of different possibilities here, and clearly I think, you know, there are advantages and disadvantages. I think that's something that probably everybody would agree with.

One thing that we didn't do, that I think in listening to some of these presentations perhaps would be the best way to deal with this, is to suggest that whatever method of masking is to be employed in the pivotal study be tested as part of the pre-pivotal or feasibility studies, and in some way validated before being used in the pivotal study. And I think that by just saying that, we could sort of eliminate the discussion, or maybe, at your discretion--

DR. BLANCO: Well, I'm not--

DR. SCHULTZ: --shorten the discussion significantly.

DR. BLANCO: As I said, we've got the video, so

I'm happy to expand it to the others. I think it makes sense to validate it before you use it, and if you can validate it, then that's the whole point. Because, again, it may be different, and different sponsors may want to do it different ways. Yes?

MR. : This raises a question for me about getting women to consent to be in the study. If you're going to approach women and say, "I'm testing a new product that has the potential to reduce your risk of getting adhesions, is anybody going to sign up for the control group? I mean, I'm concerned about that. We've had that experience in other instances where everybody wants the new stuff.

DR. BLANCO: Well, that's a problem in a lot of studies. That's something they need to deal with. I mean, that's something you have to deal with anytime--you know, we are in an age of "more is better," although that's not necessarily true, so it's often difficult to do that, but I think that's part and parcel with every randomized control trial that you do.

MR. : There are historical examples of where the placebo did better, so you have to not fall in love with your own product, whether it's a sepsis product or an adhesion product. Just a quick two examples, Thalidomide and DES, where the placebo groups ultimately were treated

better. And so you have to not, you know, sell--you can't oversell research. Research is research. Patients enter into research for the right reasons, and you leave it at that.

MR. : Before we leave this, I'm a little discomfited by how you're going to validate this. I mean, you could argue that you had two observers, as was suggested, manipulating the laparoscope, for example. They could give a score and you could average those. Or are you validating what they do or find versus what's able to be scored on the basis of a videotape. What is your--what are you--

MR. : I think that--I mean, I'll tackle that--I think it depends on what you're going to use. I mean, you could do it separate ways. You could use two observers and see what the intra-observer, you know, variability is, to determine whether that's the method that you want to use, whether it's pretty accurate. If you have video, you could have the original observer score it, have other people look at it, and then see inter- and intra-observer variability.

I mean, there are a lot of ways to validate it. I think the issue is--and I think this is the point that maybe took all day--but each study is going to be slightly different, and you're going to have to take each of the

studies and it has to be good science. I think that's the problem. It's got to differentiate that signal from the noise or, you know, it shouldn't be--it should go forth. So I think that's the way I would answer that.

MR. : So how would we handle laparotomies? We would videotape them, as well? Is that the--

MR. : Well, that would--I don't know. I mean--

DR. CHATMAN: I think one of the simplest things to do is to have a second person come in and score it. He didn't know what was there. He's a qualified observer. Particularly for laparotomy. It's a little easier for laparotomy because you have these tape options that you could choose to evoke or not. But in the case of laparotomy, the most comforting thing from a scientific point of view is have somebody else come in, score it and be done with it.

I think your point about good science, one of the problems with good science, the better the science, the more one tube, one ovary, one uterus, and the conflict that it puts the sponsors in is, now you are about to hand them some very, very--they did good science, but now you're going to reward them with a very, very limited indication. And I think that highlights the philosophic problems of whether or

not these results can be generalized. The better the science, the potential outcome is a more limited indication.

DR. BLANCO: Well, Don, I think your comment leads us right into five. I would like to go ahead and continue, unless someone else wants to make another comment about four.

Five, some studies have shown that while an adhesion barrier might work well in laparotomy, the same barrier might not work well in the laparoscopic surgical environment. Laparotomy and laparoscopic surgical procedures have many potentially different characteristics, including rates of de novo and reformed adhesions; technical aspects of adhesion barrier application; patient population; levels of hemostasis, desiccation and tissue manipulation; and presence of carbon dioxide gas.

Please discuss whether there are specific circumstances for which separate studies evaluating adhesion barriers applied during laparotomy or laparoscopy are not necessary. Who would like to begin? Nobody?

Well, I would like to address an issue, and I forgot, I think--I don't know whether it was you, Dr. Schwaitzberg, or one of the other speakers who said there are no good studies, the studies that have been quoted have been poor--oh, it was Dr. Wiseman. Thank you.

Well, I would say that all that says to me, sir,

is that it's then--the onus is on the industry, then, to prove that there is no difference, if there is no data, you know. Because as a surgeon I can tell you it's two totally different procedures, whether you proceed with a laparoscope or you do laparotomy, in terms of handling of the bowel, packing of the bowel, CO2 exposure, et cetera. That would be my first comment on this issue of laparotomy versus laparoscopy.

I think it also, again, goes back to the individual study of what is the indication that you're looking for as to whether things can be applied the same or not. I'll give you an example.

You're looking at a fallopian tube and you do lysis of adhesions of the fallopian tube, and then you put again some sort of a blanket product over it, and you're only going to look and score whether there are any adhesions around the fallopian tube. Well, at least intuitively it would not seem that in that particular case it should be a bit difference whether you do it between a laparotomy or a laparoscopy.

But if you were to look at bowel adhesions in those same set of patients as an outcome of your surgical procedure, I would expect that there would probably be significant differences because of handling of the bowel. Now, I know that laparoscopy with CO2, it may actually, you

know, create a lot of adhesions as well. But, you know, where is the data? Again, that's the issue. We've got to rely on data, and at least on looking at it, first blush, they are two radically different procedures.

MR. : And then we get more complicated, of course. There are a variety of energy sources that we use in a laparoscopy that we don't use necessarily in laparotomy: electric surgery, the--what's that, jackhammer?--harmonic scalpel; the variety of lasers that are--you know, all those are variables that just compound the potential study.

DR. BLANCO: Jerry?

DR. SHIRK: Well, the question is obviously de novo adhesions versus reformed adhesions, and I don't think there's probably any question that if you just do a laparoscopy, that your de novo adhesion formation is going to be significantly reduced. I mean, I don't know that diagnostic laparoscopy is going to create nearly the adhesions that a laparotomy is going to, and obviously I've looked back on a lot of patients I've done diagnostic laparoscopes on and a lot of patients I've done laparotomies on. You know, there's significant difference in adhesions there.

But, I mean, I think--so the question is, de novo adhesions and what you're doing de novo, versus how the

adhesion is going to react, you know, doing the procedures laparoscopically. Say if I have a patient with significant pelvic adhesions and peritubal adhesions and periovarian adhesions, basically, are those adhesions any different treated laparoscopically than by laparotomy?

You know, the answer is, probably not. I mean, you know, I don't think that laparoscopy suddenly magically changes how those adhesions are going to reform themselves. So part of the question here is basically--between laparoscopy and laparotomy is de novo adhesions versus reformed adhesions.

DR. BLANCO: Let me just add something. I would think, knowing, having done this for a while and knowing how panels work, that it would behoove industry to do either laparotomy or laparoscopy, because when you come forth with data that's mixed, if it's not clean, clean, clean and there are some differences, it's going to open up a big can of worms.

I think that's the way I would look at it. It has the potential. We've been there before, where you collect data in slightly different ways and all of a sudden there's a difference between those subsets, and then you start, "Well, is it real or not? Can you use it or not?" So I think it's just a caution. Subir, what do you think?

DR. ROY: I think it's to industry's best interest

to prove that laparotomy and laparoscopy are the same, if it is, and otherwise keep it separate until such time as you do prove it. There are just too many variables. As has been discussed, there is different irrigation solutions. You've got the CO2 on the one hand, you've got either drying or packs being placed. I mean, Victor is probably the only one I know of who has no adhesions doing laparotomies, but then--

[Laughter.]

DR. ROY: So I think it's probably in their best interest to keep them separate.

DR. BLANCO: Any other comments?

DR. ROY: Could I ask if it would be okay if Dr. DeZiarga made a comment?

DR. BLANCO: I think the panel would be agreeable to that. Please identify yourself, any affiliation and any connection or support from industry, please.

DR. DeZIARGA: My name is Gere DeZiarga. I am professor of obstetrics and gynecology at the University of Southern California. I have been working extensively in adhesion prevention research, helping develop products and understand the pathophysiology of repair since 1978. Through that period of time I have received extensive support by industry. I am a consultant for virtually--for almost all of the companies in this room, and I have

complete conflicts of interest.

[Laughter.]

DR. BLANCO: Duly noted, sir.

DR. DeZIARGA: Thank you, Jorge.

The question that I would like to respond to is one of fact. I think you very correctly challenged Dr. Wiseman and all of us, really. It's not the absence of data that drives these decisions, it's the presence of data. And if it is the case that there is evidence where an adhesion prevention device has been used both in a laparotomy and a laparoscopy for the same type of surgery at the same anatomical location, you need to hear about it, to find out if in fact there are some special circumstances where data derived from one type of approach is applicable to the other.

I would like to remind the panel that that in fact has occurred. There have been a number of studies performed and published in peer review journals with ovarian cystectomies of a variety of types, where Interceed has been applied, in some instances through a laparotomy incision, in other instances through a laparoscopic approach.

The principal laparotomy study that I cite is one that Dr. Malinak was involved with. Interceed was applied in a randomized fashion. Published in the green journal, Obstetrics and Gynecology. The principal laparoscopic

surgery done in exactly the same type of study, a randomized controlled study using Interceed with second laparoscopy, was done by George Keckstein, published in Human Reproduction.

I bring to the panel's attention that the results were congruent, virtually identical. One side was--the effect of the device was exactly the same in both studies compared to the contralateral control. And so I think there is evidence that an adhesion prevention device can be applied through both laparoscopy and laparotomy with exactly the same results, and I would suggest to the panel that there is a special circumstance, and that's gynecologic pelvic surgery. Thank you.

DR. BLANCO: Thank you, Dr. DeZiarga. And I'm glad you pointed out at the end because it's--what the congruent results were looking at, ovarian adhesions. Some of the panel's concern has to do with packing and bowel and so forth.

All right. Any other comments that the panel would like to make on this issue of laparotomy versus laparoscopy?

MR. : I just want to clear up one thing, Jorge. I mean, are we talking about the use of the device, you know, in somebody who's got adhesions and you're trying to prevent reformation, or are we talking about the use in

somebody you're operating on and basically you're trying to prevent de novo adhesions in a global fashion?

DR. BLANCO: It could be both, it could be one, it could be the other. I mean, we're trying to give some guidance as to what kind of data the panel would like to see.

Dr. Schultz, do you want to address that a little bit more?

DR. SCHULTZ: Well, I would just again like to take you back to the guidance document and hear what you have to say about the way we express this, because I don't want to leave the impression that what the guidance document says is that in every instance two separate randomized controlled trials need to be done. In fact, that's not what the guidance document says at all.

What it says is that--

DR. BLANCO: What page are you on?

DR. SCHULTZ: I am page 20, special considerations, laparotomy/laparoscopy. "Products should, in general"--and that was quoted correctly--"be evaluated separately...." Sponsors are encouraged to develop laparoscopic animal models to look at the similarities and differences between laparoscopy and laparotomy. There may be some differences, both quantitative and qualitative.

And I think there are studies which show both of

those. There are studies which show similarities and there are also studies which show differences, so I don't think that that question has entirely been laid to rest across the board. But the final comment there is that it is anticipated that existing laparotomy data could be referenced to reduce the requirements for subsequent laparoscopic indication, and I think the reverse of that is true, as well.

So I don't think what we are suggesting in this section is that across the board, two separate randomized controlled trials need to be done. What we are saying is that it is up to the sponsor, as Dr. DeZiarga pointed out, to show that the data can be extrapolated from one to the other, and not to imply that it can be extrapolated.

DR. BLANCO: Thank you. Any other comments? Dr. Carson?

DR. CARSON: I just want to be specific about that. I would think that it would be fine if a particular product is shown by the sponsor not to have a difference between laparotomy and laparoscopy, and then combine the trial, however--and extrapolate from that in that very specific product--however, not from another product. For example, I don't think the data from Interceed on ovarian surgery can be extrapolated to another soluble barrier, just to be specific.

MR. : Okay, but--go ahead.

MR. : Maybe you were going to say the same thing. I think what wasn't said by Dr. DeZiarga was that there were also no upper abdominal adhesions or any de novo adhesion differences between the two studies, probably because they might not have been looked for. Which is, therefore, not to say that they are the same, which otherwise might be implication be concluded. But I think unless you look for it and don't find it, you can't assume that it's not there.

MR. : Yes. I mean, I'm not arguing that point. Again, I'm not saying that--I mean, I think what the guidance is saying is that it is in fact up to the sponsor to show that the data could be extrapolated from one to another. What I am saying is that I think that we have shown some flexibility in terms of saying that once you have demonstrated efficacy in one model, that you can look at that data and apply it to the other model without having to go back to ground zero. That's the only point that I'm making.

DR. SHIRK: So what you're saying is basically if they do a study by laparotomy and then if it's still indicated, then do they have to go back and do a separate study then to say then you can apply this laparoscopically, or can it be applied immediately laparoscopically? You

understand what I'm trying to say?

Say you have an agent and basically you prove that it doesn't--it has great adhesion information, you get it through and you're applying it, but it can be applied fairly easily laparoscopically. Then do they have to go back and do a study to show that it can be applied laparoscopically, or can they just say go ahead, and can the surgeon then apply it laparoscopically?

MS. : Jerry, the guidance document says less data would be required. In that case, maybe you don't need so much data. You don't have to do the full-scale thing again, but you've got to demonstrate it.

DR. SHIRK: Okay, so it would be two separate studies. That's what I'm trying to get--that was what my question is. Are we separating this thing into two separate studies, so if they get approved laparoscopically it's only approved for laparoscopic use and not approved for laparotomy use? Or if it's approved for laparotomy use, is it not approved for laparoscopic use? Are they two separate items, or are we saying that they go hand-in-hand? Okay?

MR. : I think, if I interpret the guidance correctly, what it's saying is that there are two separate questions. Okay? Two separate, let's say two separate parts of a question which need to be answered individually, but in the way that they are answered, the

data from one answer could in fact apply, at least in part, to answering--to the other answer. Does that make sense? I mean, I think that that--

DR. SHIRK: I understand what you're saying, but--

MR. : I mean, I think that there is a correlation. I think what we're saying is, we expect there to be a correlation between the efficacy recorded for laparotomy and laparoscopy. But I think, as was stated earlier, you know, the devil is in the details, and if the amount for laparotomy is this and the amount for laparoscopy is this, as we've said before, this may be okay, this may not be okay. So I think that there needs to be some additional information to show that the--both in terms of safety, in terms of feasibility, i.e., the ability to apply the device, and in terms of efficacy, that the results would be comparable.

DR. BLANCO: Yes. I think the issue is, you do have to have some data. As you say, you've got to have some details to see where the devil is. I think Dr. DeZiarga quoted the two stories, two stories with Interceed, but I believe there's a story that's not published, that was a follow-up that got stopped because it didn't quite show the same kind congruence. I believe Dr. Diamond participated in that study. I wonder if he would like to comment on that?

DR. DIAMOND: I'm not sure I can really comment on

that.

DR. BLANCO: Okay. We'll let it go at that, but I think that there needs to be--I think again it's important for industry to realize that there has to be data to evaluate, to be able to lump things together.

Anything else on laparoscopy/laparotomy?

[No response.]

DR. BLANCO: Well, if not, we seem to be moving right on along this afternoon.

Number six: Sponsors of adhesion barrier products under development are currently requested to provide information on the potential of an adhesion barrier to enhance infection already present in the abdomen through contamination, bowel perforation, incision dehiscence, et cetera. What are the clinical implications of findings of enhanced infection in the presence of the adhesion barrier? Would you recommend specific labeling to address this issue?

Who would like to begin with that one?

Oh, I'm sorry. Don, did you have--I started talking and I forgot about you. Did you have an issue on the other one, number five?

DR. CHATMAN: Well, no, just a comment. If--

DR. BLANCO: Please do that.

DR. CHATMAN: --the literature is mixed and opinions vary as to whether or not laparoscopy differs from

laparotomy, then maybe we should ask the investigators to give us that data beforehand. That's the only comment.

DR. BLANCO: You know, the problem--I guess in answer to that comment--is that there is a lot of--as I think we heard yesterday in other meetings, some data never gets published because it doesn't necessarily show what people hoped it shows.

DR. CHATMAN: We can't comment, then, can we?

DR. BLANCO: We can't comment on that, but it just makes it interesting to wonder whether things are so applicable. So we'll leave it at that.

All right, number six, anybody want to start with that? Please.

MR. : I read it as a safety issue so, I mean, obviously it has implication in the risk/benefit analysis that you would be doing to take the product to approval. I'm not sure I know what else. Is there something secret in the question?

DR. BLANCO: I don't think there's any secret.

[Laughter.]

DR. BLANCO: I think it's probably just the easiest ones to go at. Basically, if it causes infection, that's bad.

MR. : Or if it makes infection worse.

DR. BLANCO: Yes, if it makes it worse, that's

bad.

MS. : That's bad.

MR. : You definitely wouldn't use it. I mean, you wouldn't approve it for use under that condition and you would prohibit its use--

DR. BLANCO: Yes. I mean, I don't think--

MR. : --if it were approved for other indications.

DR. BLANCO: I don't think it's a matter of labeling. I think it's a matter of you wouldn't want to approve it, if it's--

MR. : I think it would definitely come into your risk/benefit and you would never get to approve it.

DR. BLANCO: I think that's it. I don't know, does anybody want to make any other comment on it now? It's pretty straightforward.

MR. : Could I ask just one question in that regard?

DR. BLANCO: Please.

MR. : If you're going to do an inguinal hernia repair and you sew it up, the infection rate is approximately a percent or less. If you use a polypropylene patch, which is the standard today, the infection rate is well known to be higher than that. So here's an example of

a surgical technique that's used all over America, where clearly the use of the device, which has a benefit in reducing recurrence, is associated with an increased infection.

Now, I'm like "Mr. Infection." I would never approve it, either. But you could conceive of some circumstances where you would scratch your head, and we clearly accept clinically a slightly increased infection rate. So any important difference obviously is a no-brainer. The product is dead in the water.

But I think you also, before you just kill things, you have to say, "Is this meaningful?" If this was a super product where adhesions were eliminated from 90 to 10 and infection rates were increased from 1 to 2, there are some instances where you might turn around and say, all right.

DR. BLANCO: I don't think the panel would argue with that. As a matter of fact, that's basically in the--

MS. : Risk/benefit.

DR. BLANCO: --well, it's in the FDA mandate. What you try to do is, you see a clinically significant effect that outweighs, you know, a risk, whatever the risk of the procedure. So absolutely, I think if you were able to demonstrate sufficient clinical benefit, you know, they would accept a higher risk, as opposed to if you have a higher risk and little or marginal clinical benefit. I'm

sorry that we took it so light.

MR. : I did say risk/benefit in my response to it, so it's in the transcript.

DR. BLANCO: Now I have an interesting question, and we'll get your thoughts on this. What about if you're not in human trials yet and you identify some risk at the animal level? Would you continue to investigate that?

MR. : You know, I think--and that's--

DR. BLANCO: That's a double-edged question.

MR. : Yes, it is a double-edged question, I think, and it has come up, you know, in the past. I think significant increases in infection in an animal model would make anybody in this room uncomfortable about proceeding with humans. I mean, although we let things go in the reverse, if it looks okay in the animals, we may still see infections in people, but nobody--and animals are all Darwinially selected. They're all kind of tougher than we are. And so if you have--they're all sort of a best case scenario. If it can't survive the best case scenario, in my opinion I wouldn't feel comfortable. I wouldn't put it in a patient.

DR. BLANCO: Anybody else? Yes, go ahead.

MS. : I just have to--you know, it reminds me of beagle dogs and Depo-Provera. I mean, women were deprived of a very, very good contraceptive because of

an idiosyncratic in the--it is syncracy in the biology of beagle dog breasts. So I think each individual adverse effect has to be approached differently.

MR. : Well, I would agree that if you find it in the rat, then maybe the sponsor in their preclinical tries it in rabbits and--I mean, there are mechanisms for saying, "Okay, well, this was idiosyncratic," and that you wouldn't--they wouldn't necessarily stop it. If they find it's a common effect, they wouldn't proceed.

DR. BLANCO: All right. I think we've finished with the questions, but I'm going to take the--oh, I'm sorry, Subir. You want to make another comment?

DR. ROY: Could I just ask, does--I forget from reading this document--is there any provision for carrying animal studies through to primate models, in terms of safety, before they are brought into human studies?

MR. : ...models are, but the current models, there has not been a clinical reversal of what has been safe in animals to be not found safe in people.

DR. BLANCO: Yes, ma'am?

MS. : I would like to know if there are any gender issues as far as adhesions are concerned, that would make the devices applicable to--in other words, could the guidance document cover the applicability of these devices to men as well as women?

MR. : Well, you've raised an interesting question because the best models of adhesion reformation will all occur in women because men don't have pelvic surgery, so there is a potential gender bias against men because there won't be very good models of adhesion reformation in men, and women will be the beneficiaries of having adhesion reformation studied because of the gynecologic approach. It's a reverse bias against men.

DR. BLANCO: All right. Anyone else care to make a comment?

MR. : But that doesn't answer the question. Do we know whether there is a gender predilection for adhesion formation? Do we even know that it makes a difference in a reproductive age woman when she undergoes her surgery and whether she is on any sort of immune modulating substances?

MR. : Including her own hormones?

MR. : Right.

DR. BLANCO: Okay. I'm going to take the prerogative of the chairman, now that we've gone through all of the questions, and I would like to, since we're being very inclusive of both industry and our visiting experts, that we appreciate their input, I thought that we would have each of the individuals, if they care to, that presented before the panel, come in and take three minutes to say

some--have some comments on the day's panel deliberations, if they care to.

Dr. Burns, are you still here? Would you care to? And do try to limit--wait until you come to the microphone--but please try to limit it to just a few minutes.

DR. BURNS: Jim Burns from Genzyme Corporation, on behalf of the Ad Hoc Task Force. I hadn't really thought about coming up with something, but a lot of things have been going through my mind through this discussion and I've been having some short discussions with some of my colleagues.

I think one of the things is that I was happy to hear and I think we were all happy to hear that adhesion prevention can be an important endpoint, in and of itself. And I think that was a message that we did hear, and if that is something that can be expressed in the guidance document, that would be of great assistance to us as sponsors who develop products, to know that that is an outcome worthy of designing clinical trials.

I think one of the things that's very often easy to overlook for others, other than those that are involved in developing these products, is that there is a finite population which will allow you to determine whether these products are effective for adhesion prevention or not. You know, that's a battle that we have to face.

But, nevertheless, in the design of these trials it is something that we struggle with, and we look for guidance from not only the panel members but also from the FDA, to allow us to be able to design these studies to best get these products in the hands of surgeons and to help patients. That's what we're here for. We ultimately hope that whatever comes out of this discussion of the guidance document, that it's for ultimately the good of the patient.

Thank you.

DR. BLANCO: Thank you very much.

Dr. Wiseman? I'm just going in the order that folks came up.

DR. WISEMAN: Thank you. Dr. David Wiseman. Just a couple of brief comments.

First of all, there was some discussion on looking at different sites within the abdomen and so on, and there is a practical solution to that discussion. That is, when a liquid agent is going to be used, the types of clinical studies that have been performed will automatically look at a number of different sites within the abdomen.

So a liquid agent, there are two or three now that have been studied and clinical studies have been described publicly. They do, they have indeed looked at large bowel, small bowel, posterior uterus, anterior uterus, ovary, omentum and so on. So, practically speaking, that probably

comes solved during that type of study.

The other kind of product which is more site-specific, of course they only look at ovaries or uterus or wherever it has been studied, and of course that's the case where our discussions of extrapolation come in. The only problem there which could conceivably come up is, does the product move or not?

And so, because it is a site-specific agent, again that's something that can be studied certainly in animals. And secondly, by implication of peritoneal healing being similar throughout the cavity, one might be able to make extrapolations, given the caveats that we expressed earlier.

Briefly, to come back to the laparoscopy issue, I think we have to be very careful about defining de novo adhesions. Dr. Diamond has eloquently described two types of de novo adhesions. They have what is called 1-A, the type 1-A, which are the incidental adhesions that are due to desiccation and retraction and so on, and we have reason to believe that those type of adhesions are indeed reduced in laparoscopy.

But the other kind of adhesion, the type 1-B de novo adhesion, which is the adhesion that is caused at direct site of surgical manipulation, say a myomectomy or an ovarian cystectomy, in contrast, just to clarify the chairman's statements, it's not that we have--there is an

absence of data. We have data.

The data says that there is no difference or there is substantially no difference between the rates of development of type 1-B adhesions in laparoscopy and type 1-B adhesions in laparotomy. So there is that data, and a similar statement can be made for reformed adhesions. They appear to form at the same rate, and we have data, and we have done a meta analysis to say that they form at substantially the same rate in the two situations.

And then to Dr. DeZiarga's comment, to expand on his comment, there are in fact four Interceed studies which replicate the--which were performed in laparoscopy, which replicate the findings that were done in laparotomy in several situations, one being the cystectomy that Dr. DeZiarga alluded to; second of all, cul-de-sac endometriosis; third of all, myomectomy; and the fourth one I think was ovarian procedures. That was a Walwema study that was published from Germany.

Lastly, Dr. Schultz referred to some studies that suggest there are differences, and perhaps after the meeting I would be very interested to have a discussion or at least a listing of those studies, because that's something that we need to get into. And to cite non-published data I think is a little unfair on us, that we're running around with our hands behind our back.

The study that you alluded to, Mr. Chairman, was a study with Interceed where, to my understanding, this was a "Dear Doctor" letter that was written. The Interceed was wrapped around the ovary and the tube, the ovary and the tube were wrapped together, and whether you do that in laparotomy or laparoscopy, I think that would be an excellent way of making adhesions that could be accomplished both in laparotomy and laparoscopy. So I'm not sure that that study can be used against the argument that the behavior of the material is different in laparotomy and laparoscopy.

Thank you.

DR. BLANCO: You're welcome. The only other comment I would make would be that if data is unpublished because it doesn't show what it was set to do, that doesn't mean it doesn't exist. We'll leave it at that.

Dr. Gomel, would you like a chance to speak?

DR. GOMEL: Thank you very much, Mr. Chairman. I will simply reiterate one or two points that have already been made by Dr. Wiseman.

And that is, at the injury site or surgery, whether the surgery is done by laparoscopy or by laparotomy, the adhesions appear to be the same, both in animal and human studies. The only difference appears to be in the rate, quantity of de novo adhesions which are adhesions at

sites other than the surgical site, which appear to be greater in number and in extent in laparotomy, but that is because there is injury that is being done involuntarily to those other sites.

Whether it is by packing or by touching or by manipulating bowel, it is still an injury, or injury by desiccation, which also occurs in laparoscopy because of the large quantities of CO2 we put through in operative laparoscopy. But evidence shows that there are more de novo adhesions at sites other than the surgical site. And again, reformation of adhesions appears to be pretty well at the same rate by both laparotomy and by laparoscopy.

Because of these facts, documented facts, I do not believe that it is necessarily--it is necessary, I should say, that a study be performed both at laparotomy and at laparoscopy. If one is using a site-specific product, provided the product can be applied equally well by laparoscopy and by laparotomy, I really do not see, unless you can show me strong evidence, that you need to repeat the study at laparoscopy as well.

Thank you very much.

DR. BLANCO: Thank you, Dr. Gomel.

Dr. Carson would like to make a comment.

DR. CARSON: Along those lines, it is possible that if we put a product, a biochemical product in the

abdomen, and the acidic effect of carbon dioxide changes the property of that molecule or of that product, it could have let's say an acidic effect all over the bowel that similar-- and cause de novo adhesions from that acidic effect that you might not see in a laparotomy. And therefore, unless you show beforehand that the laparotomy and the laparoscopy effects are the same, once the product is in or after administration of the product, you can't tell.

DR. BLANCO: Thank you.

Dr. Malinak?

DR. MALINAK: No further comment.

DR. BLANCO: Thank you, sir.

Dr. Diamond?

DR. DIAMOND: Thank you, Jorge. Michael Diamond, Wayne State University, again.

First I would like to thank FDA, Dr. Schultz, Colin Pollard, Elisa Harvey, Diane Mitchell, for really taking the initiative to put together a guidance document, because I think that will be very helpful to the panels in the future as they go to evaluate, to clinicians and to industry as well, and I think that proactive effort should be recognized.

There were a couple of other comments that were made during the course of the day that I just wanted to allude to and share some of my thoughts. First, one that

has been approached twice already, one place a number of times got bogged down here, and in fact in the literature even, if you go back to the early nineties, we got bogged down, is talking about de novo adhesion formation and adhesion reformation. And that in fact is why we came up with the 1-A, 1-B, 2-A, 2-B, because people were using the same terms to mean very different things, and so I think we need to be very careful about that.

But I would agree with the comments that Dr. Gomel and Dr. Wiseman have shared with you, that for de novo adhesions at surgical sites, 1-B, and for reformation, I think the data is fairly convincing that there is no difference in subsequent adhesion development. And if you think about it, if you're taking out a uterine fibroid, regardless of where you're getting into the abdomen, laparoscopy, laparotomy, ovarian cystectomy, or lysing an adhesion between the ovary and the uterus, you're doing the same thing. It's just a different mode of entry into the cavity.

Now the question Dr. Carson brings up is, will a CO2 environment impact upon an adjuvant being utilized to reduce an adhesion, I think is an important question that will need to be addressed. But the adhesions themselves as a function of surgical modality, I think there is a fair amount of data.

Site-specific issues, that came up a couple of times. I think there is beginning to be some data suggesting that there might be some variations in sites throughout the abdominal cavity. We have some data that we presented at several meetings over the last couple of years looking at the molecular biology level, at growth factors, an activator, proteases, which suggests that there are differences at different sites.

Having said that, I think there is opportunity to extend at least somewhat from sites. If, for example, you're looking at parietal peritoneum, the anterior abdominal wall in the midline, I think that probably can be extended to the sides and then to the pelvis. So I think there is some extensions that can be made from a site-specific point of view.

With regard to the issue of video review, I happen to--review and how you assess it, I think video review is probably the best way to go because you don't--if you have a second observer come into the operating room, you then have 200 people, the average size study, trying to give observations, and the reproducibility there I think is much poorer than you would with a video review.

In contrast, though, to what Dr. Carson recommended, I would not have a narrative component to that because the person doing the narration knows whether it was

a treated patient or a control patient, and some bias can get through even if they don't mention specifically what the group assignment was. Similarly, I would have that done in the absence of any kind of case report from the surgeon, so that you are not biased because the surgeon thought it was 5 centimeters or 50 percent. It's much easier to go along and say, "Yes, that looks about right," than having as a blind reviewer to say 40, 50 or 60. And so I would have the blind reviewer doing it blind or masked, whichever is the appropriate term.

Lastly, Dr. Roy asked a question about women and about men, and in fact we do have some data that is available to that now. In the Seprafilm study that was done in general surgery, that report was published several years ago, we found out--these were patients who had either ulcerative colitis or familial--who underwent colectomy with creation of a diverting ileostomy, and second-look was subsequently at the time of looking in through that ileostomy site and looking at the midline incision to see whether or not there were adhesions there.

What that study showed is that, first of all, in the women their instance--in the control groups, the control group overall, the instance of adhesion was about 94 percent of the subjects, so adhesions were ubiquitous in those populations as well, not something specifically unique to

infertility patients or to young women. Secondly, and now you get into smaller numbers, but when the analysis was done to look at men versus women, in fact if anything there was a higher rate of adhesion development in the men than there was in the women in that study.

Thank you.

DR. BLANCO: Thank you, Dr. Diamond.

Dr. DeZiarga?

DR. DeZIARGA: Gere DeZiarga. Jorge, actually I think it's all been said. I just want to leave, as sort of the grand old man of adhesion prevention, having done this and worked with the FDA in a very positive and productive way since the late 1970s, that I think the guidance document that the Ob/Gyn Devices people have put together has brought a very important focus and a very timely one to what really is the largest unmet need of surgical therapeutics for patients of the obstetrics and gynecologic group.

I think this guidance document, Elisa Harvey, Diane Mitchell, Colin Pollard, especially Dan Schultz, who brought it to our attention, is a major contribution, and I would like to commend them on that publicly. I know I speak for many in so doing.

I would also like to close by congratulating you, Jorge, and your panel in generating conversation which I think has been stimulating and very meaningful and will add

continued value to this process, and will benefit all of our patients in the years to come.

Thank you.

DR. BLANCO: Thank you. I would actually like to have Dr. Schwaitzberg have a minute to say something if he wants, and then if any of the panel members, and we'll close after that.

DR. SCHWAITZBERG: I would like to echo some of the comments about how important and illustrative this process is. This room is mostly made up of gynecologists, and so I would like to make one last appeal for my general surgery brethren that are under-reported here today.

I don't know of any mechanism for which we will be able to study adhesion reformation, bowel-to-bowel adhesions in the general surgical model, which is an incredibly important model to us as general surgeons. And I would hope that--and I got the message loud and clear, animal studies are not all that provocative to the panel--but I would hope that someday we will be able to create a rigorous enough model that will be convincing enough that we will be able to add indications to the future to help the untold numbers of general surgical patients who need indicated adhesion formation prevention. That is a much tougher problem to study, you know, in the years to come.

I have enjoyed my opportunity to have the floor.

I'm grateful for that opportunity, as well, and I think you've done a fantastic job. Thank you.

DR. BLANCO: Thank you, sir.

Anyone from the panel care to make any comments?

[No response.]

DR. BLANCO: Dr. Schultz? Your turn.

DR. SCHULTZ: I would just like to say, echo what has been said in terms of thanking all the participants. We appreciate the fact that you came here in the dead of winter to help us with a very difficult problem.

I would like to say and again echo what Dr. Schwaitzberg said, that we did expect and we did get a very OB/GYN loaded, if you will, perspective today. We would anticipate getting additional comments from the general surgery community. We expect, we welcome those comments. Whether or not this guidance will be taken to a separate panel, I can't say at this particular time. I would certainly welcome the opportunity to do that, but that may not be entirely my decision.

But certainly, you know, I think we wanted to start at least, and I think this is a start, getting this document out into the public where people other than those behind our four walls, arguing with each other, could see it, could argue about it, could make comments on it, and could get it hopefully into the people's hands that need it,

i.e., the industry, the investigators who are faced with the very difficult challenge of performing these studies. And I think if anything has come through loud and clear today, that has certainly been it. So we hope to expand into additional communities.

As far as the animal models are concerned, let me just close with one thing. I think you mentioned the fact that the panel was not particularly excited about those. I would add that it wasn't just the panel that had comments to make about that. And, again, I think that that is the important part of this kind of a meeting where you don't get just the perspective of FDA, the perspective of the panel, but we get to have your perspectives as well.

So, again, I thank you all very much, and I hope we can do this again sometime, maybe in the spring.

DR. BLANCO: And I would like to thank all the panel members, I would like to thank all the members of the FDA team, and I would like to thank all the audience for their excellent participation. I appreciate it, and I hope you all can go home safely. Thank you very much. The meeting is adjourned.

[Whereupon, at 5:00 p.m., the meeting was adjourned.]

CERTIFICATE

I, **ELIZABETH L. WASSERMAN,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Elizabeth L. Wasserman

ELIZABETH L. WASSERMAN